

Claims

1. A non-human animal having a mutated LAT gene coding for a mutant LAT protein, wherein said mutant LAT protein leads to an exaggerated T_H2 cell differentiation.

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2. The non-human animal according to claim 1, wherein the sequence of said mutant LAT protein corresponds to a wild type sequence and contains a single mutation of the tyrosine corresponding to Y136 in the mouse LAT protein.

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3. The non-human animal according to claim 2, wherein said mutated LAT gene coding for a mutant LAT protein comprises exon 7 of the mutated gene (SEQ ID No 2).

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4. The non-human animal according to claim 1, wherein the sequence of said mutant LAT protein contains a composite mutation of the three distal tyrosine residues.

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5. The non-human animal according to any of claims 1 to 4, wherein said non-human animal is a mammal.

6. The non-human animal according to claim 5, wherein said mammal is a rodent.

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7. The non-human animal according to claim 6, wherein said rodent is a mouse.

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8. The non-human animal according to any of claims 1 to 7, wherein said mutation consists in the replacement of the tyrosine by a residue preventing the association of the "tyrosine-based" sequences with the SH2 domain of proteins.

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9. The non-human animal according to any of claims 1 to 7, wherein said single mutation consists in the replacement of the tyrosine by a phenylalanine (Y-F), an aspartic acid (Y-

D) or a glutamic acid (Y-E).

10. The non-human animal according to claim 9, wherein said single mutation consists in the replacement of the tyrosine 5 by a phenylalanine (Y-F).

11. The non-human animal according to any of claims 1 to 10, wherein said non-human animal is homozygous for the mutated LAT gene or carries a null allele of the LAT gene.

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12. The non-human animal according to any of claims 1 to 11, wherein said mutated LAT gene is incorporated into the animal genome by targeted insertion in order to keep said mutated LAT gene under the control of regulatory regions of 15 the endogeneous LAT gene.

13. A germ cell or somatic cell from a non-human animal according to any one of claims 1-12 or any progeny thereof containing the mutated LAT gene.

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14. Use of an animal according to any of claims 1 to 12 as a model of allergy, asthma, eosinophilia and/or disease associated with TH2 cell deregulation.

25 15. A method of screening for a drug for treatment of allergy, asthma and/or disease associated with TH2 cell deregulation comprising the step of subjecting animals according to any of claims 1 to 12 which are administered with the drug to a comparison with said animals, not 30 administered with the drug.

16. A method of screening for drugs for treatment of allergy, asthma and/or disease associated with TH2 cell deregulation comprising the step of:

35 1) administering a candidate drug to a non-human animal according to any of claims 1 to 12;
2) evaluating the effect of said drug on the symptom or sign

of allergy, asthma and/or disease associated with T_H2 cell deregulation; and
3) selecting the drug that reduces said symptom or sign.

5 17. The method according to claim 16, wherein said effect of said drug can be evaluated by measuring at least one parameter selected from the group of IgE level, IgG1 level, interleukin level (IL-4, IL-10, IL-5 and/or IL-13), and eosinophilia.

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18. The method according to claim 17, wherein said effect of said drug can be evaluated by measuring the serum level of IgE and/or IgG1.

15 19. A method of screening drugs for treatment of allergy, asthma and/or disease associated with T_H2 cell deregulation comprising the step of:

1) subjecting cells according to claim 13 to a candidate drug;
20 2) evaluating the effect of said drug on said cells;
3) selecting the drug having the desired effect.

20. A method of screening for drugs for that regulate the activity of T_H2 cells, comprising the step of:
25 1) administering a candidate drug to a non-human animal according to any of claims 1 to 12; and
2) selecting a drug that modulates the activity of T_H2 cells in said non-human animal.

30 21. A method of producing a pharmaceutical composition for treating a disease associated with deregulated T_H2 cells activity, particularly asthma or allergy, the method comprising (i) selecting, identifying, optimizing or characterizing a compound using a screening method according
35 to any of claims 16 to 20 and (ii) conditioning said compound, or a derivative thereof, in a pharmaceutically acceptable carrier or vehicle.

22. A bioreactor for a large scale production of human IgE antibodies comprising an animal according to any of claims 1 to 12.

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23. A method of production of human IgE antibodies comprising the steps of :

- 1) providing a non-human animal expressing humanized IgE;
- 2) breeding said animal expressing humanized IgE with a non-
10 human animal according to any of claims 1 to 12;
- 3) immunizing the animal of the progeny with an allergen;
- 4) recovering humanized IgE specific to said allergen.

24. The method according to claim 23, wherein the step 4
15 comprises the step of producing B cell hybridomas producing said humanized IgE specific to said allergen.

25. A B cell hybridoma obtained by the method according to
claim 24.

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26. A mutated mouse gene coding for a mutant LAT protein, the sequence of which corresponds to a wild type sequence and contains a single mutation of the tyrosine Y136.

25 27. A mutated mouse gene coding for a mutant LAT protein, the sequence of which corresponds to a wild type sequence and contains a composite mutation of the three distal tyrosine residues.

30 28. The mouse gene according to any of claims 26 to 27, wherein said mutation consists in the replacement of the tyrosine by a phenylalanine (Y-F), an aspartic acid (Y-D) or a glutamic acid (Y-E).

35 29. The mouse gene according to 28, wherein said mutation consists in the replacement of the tyrosine by a phenylalanine (Y-F).

30. The mouse gene according to 26, wherein the sequence corresponds to sequence ID N°1.

5 31. The mouse gene according to 30, wherein the sequence contains exon 7 of the mutated gene (SEQ ID N°2).

10 32. A diagnostic method for asthma, allergy, eosinophilia and/or T_H2 cells deregulation comprising the detection of a mutated LAT gene coding for a mutant LAT protein containing a mutant LAT protein containing a single mutation of the tyrosine Y132 or a composite mutation of the three distal tyrosines Y171, Y191 and Y226.

15 33. A diagnostic kit for asthma, allergy, eosinophilia and/or T_H2 cells deregulation comprising oligonucleotide probes for the detection of a mutated LAT gene coding for a mutant LAT protein containing a single mutation of the tyrosine Y132 or a composite mutation of the three distal 20 tyrosines Y171, Y191 and Y226.

34. A non-human animal resulting from the breeding of a non-human animal expressing humanized IgE with the non-human animal according to any of claims 1 to 12.